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13. ABSTRACT (Maximum 200 Words)

New chemotherapeutic agents are needed for the improved treatment of breast cancer. In this proposal, we disclose a new approach to the design of anti-cancer drugs. Our method is to synthesize new drug conjugates that incorporate: (i) a specific breast cancer cell - targeting component; (ii) a rapid cell membrane translocating /nuclear localization moiety and; (iii) the capability to counter multi-drug resistance mediated by P-glycoprotein and related cellular efflux pumps. The conjugates are prepared in a few synthetic steps from available components. The goal is to demonstrate a proof-of-concept of the effectiveness of this multi-functional drug hypothesis.

Specific cancer cell-targeted compounds have been prepared from the breast cancer drug doxorubicin. This cytotoxic agent is covalently linked to a synthetic arginine-glycine-aspartic acid peptidomimetic, which recognizes and binds to $\alpha_v\beta_3$ integrin. This receptor is overexpressed on the surface of breast cancer metastatic cells and tumors. The design also includes incorporation of the Tat peptide analog, $H_2N[arginine]_7COOH$, as a rapid cell membrane translocation and effective nuclear localization moiety. The new drugs are being evaluated in breast cancer cell-lines *in vitro* and *in vivo* using human breast cancer xenografts in nude mice.

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A. Introduction

In this program, we are examining a new approach to the design of anti-cancer drugs that is directed toward (i) improving cytotoxic action against cancer cells, (ii) reducing unwanted systemic side effects, (iii) counteracting multi-drug resistance, and (iv) targeting and destroying metastatic cells as well as tumors more effectively.

Our plan is to synthesize new drug conjugates that incorporate a specific breast cancer cell targeting component, a rapid cell membrane translocating/nuclear localization moiety, and the capability to counter multi-drug resistance mediated by P-glycoprotein and related cellular efflux pumps. The conjugates will be prepared in a few synthetic steps from available intermediates. The goal is to demonstrate a proof-of-concept of the effectiveness of this multi-functional drug hypothesis.

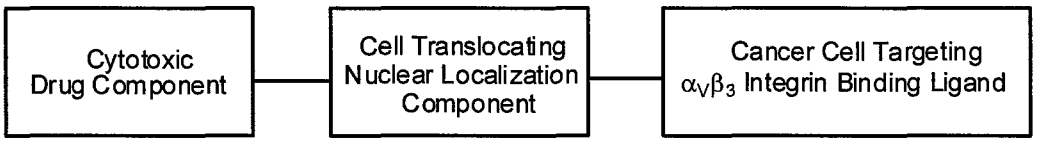
Specific cancer cell-targeted compounds are being prepared from the breast cancer drug doxorubicin. This cytotoxic agent is covalently linked to a synthetic arginine-glycine-aspartic acid peptidomimetic, which recognizes and binds to $\alpha_V\beta_3$ integrin overexpressed on the surface of breast cancer metastatic cells and tumors. The design also incorporates the Tat peptide analog, $H_2N[arginine]_7COOH$, as a rapid cell membrane translocation and effective nuclear localization moiety. Because the targeted conjugates will be rapidly directed into the cell nucleus for efficient cytotoxic effects, the drugs may escape cytoplasmic cleansing, which is mediated by cellular efflux pumps thereby abrogating an important multi-drug resistance mechanism. The new drugs will be evaluated in breast cancer cell-lines *in vitro* and *in vivo* using human breast cancer xenografts in nude mice.

B. Body

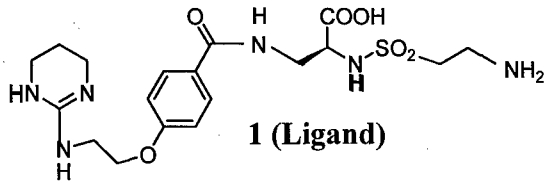
This section describes research accomplishments to date associated with the tasks outlined in the original award application.

Task 1. Synthesize several covalent conjugates utilizing the anti-tumor drug doxorubicin, which are linked to a cell translocating/nuclear localizing arginine peptide and a selective breast cancer cell targeting ligand, as well as appropriately linked components as controls **(Months 1-18)**

The three-component conjugates are being assembled according to the arrangement shown below.



Last year, as reported in our second annual report, we prepared and evaluated in cell cytotoxicity assays the compounds shown in **Figure 1**. These conjugates were based upon the relatively low affinity RGDS peptide $\alpha_V\beta_3$ integrin ligand. During this reporting period, we have now synthesized analogous doxorubicin conjugates using high affinity $\alpha_V\beta_3$ ligand **1**[1],



1 (Ligand)

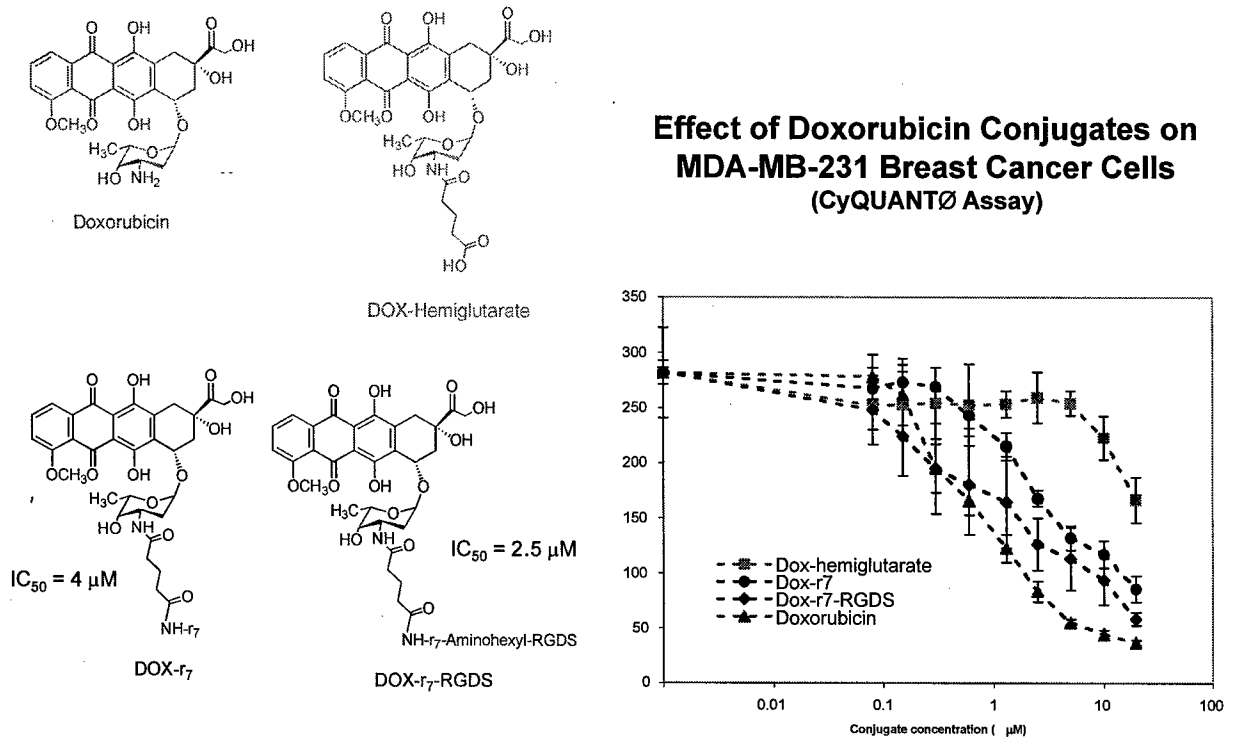
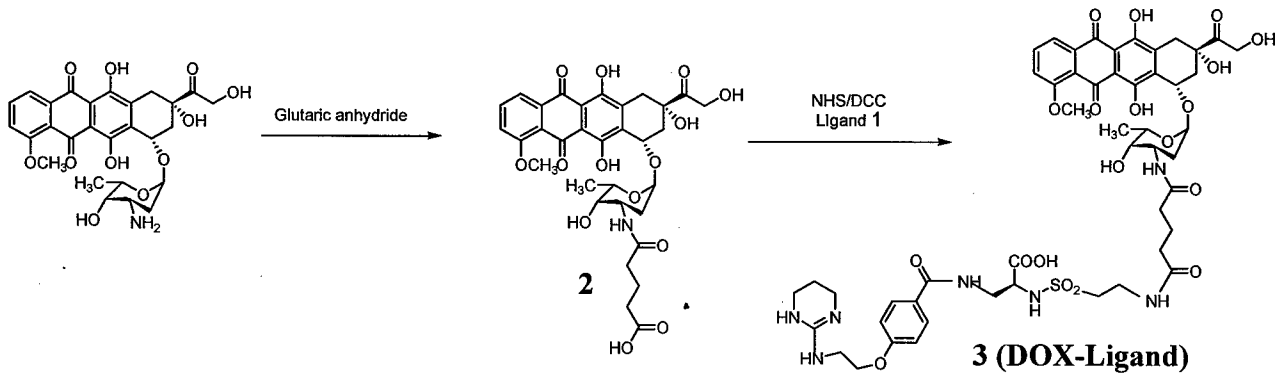


Figure 1

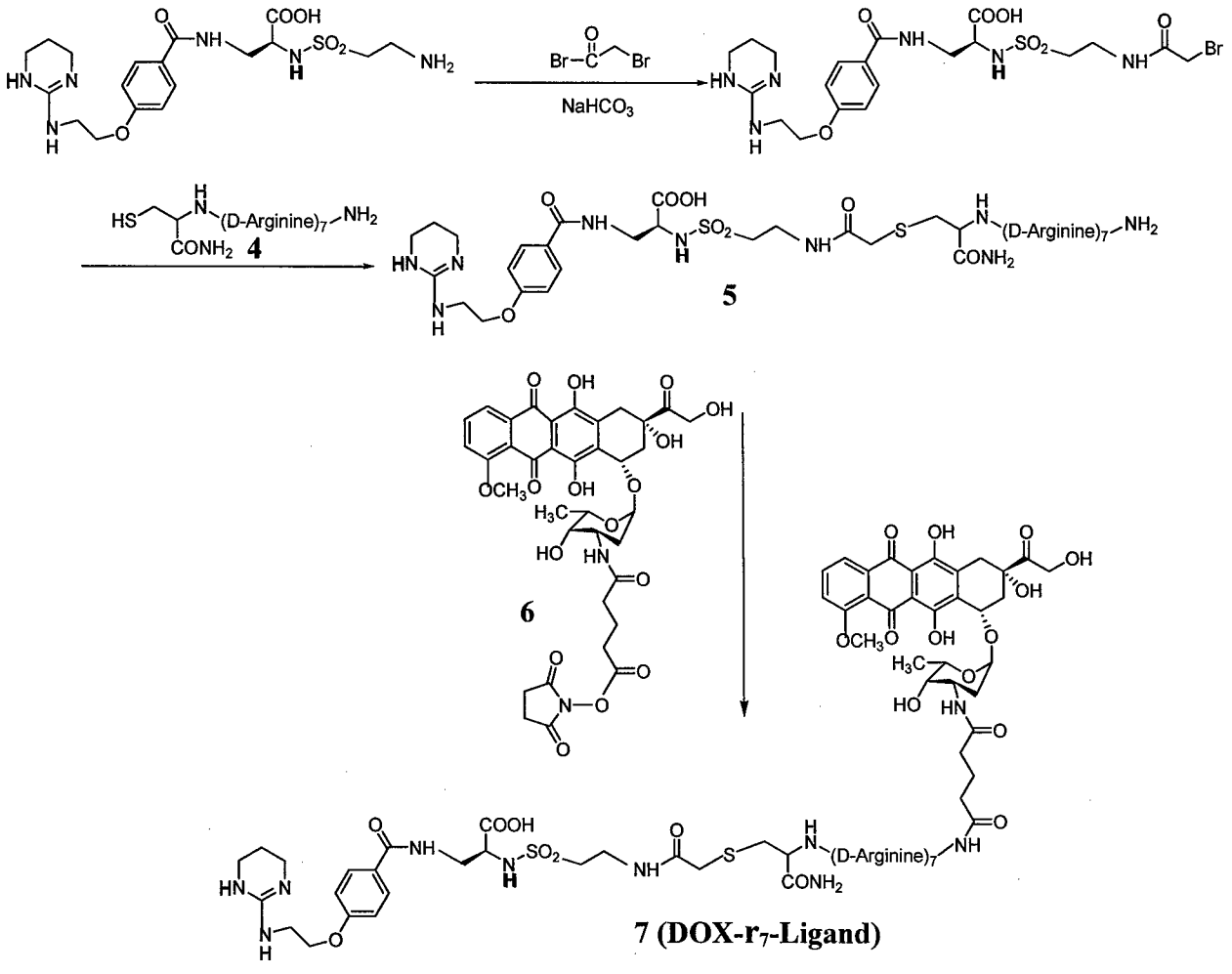
which was prepared by graduate student Jiang Sha late last year (**Scheme 1**).



Scheme 1

Doxorubicin hemiglutarate **2** was condensed, after carbodiimide activation, with **1** giving DOX-ligand conjugate **3**.

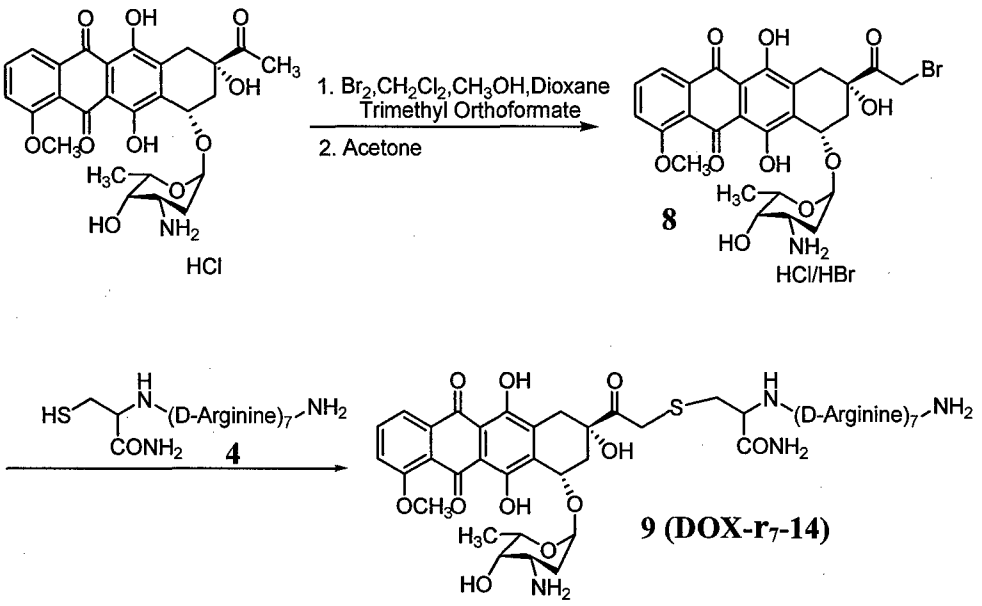
The conjugate related to **3**, but incorporating a cell translocating $(arginine)_7$ functionality, required a modified synthesis (**Scheme 2**). In this case, **1** was derivatized with a bromoacetamide moiety. This in turn allowed conjugation to the thiol-containing arginine oligomer **4** leading to **5**. Finally DOX-r_7-Ligand **7** was prepared by linking **5** with DOX-hemiglutarate via preformed NHS ester **6**.



Scheme 2

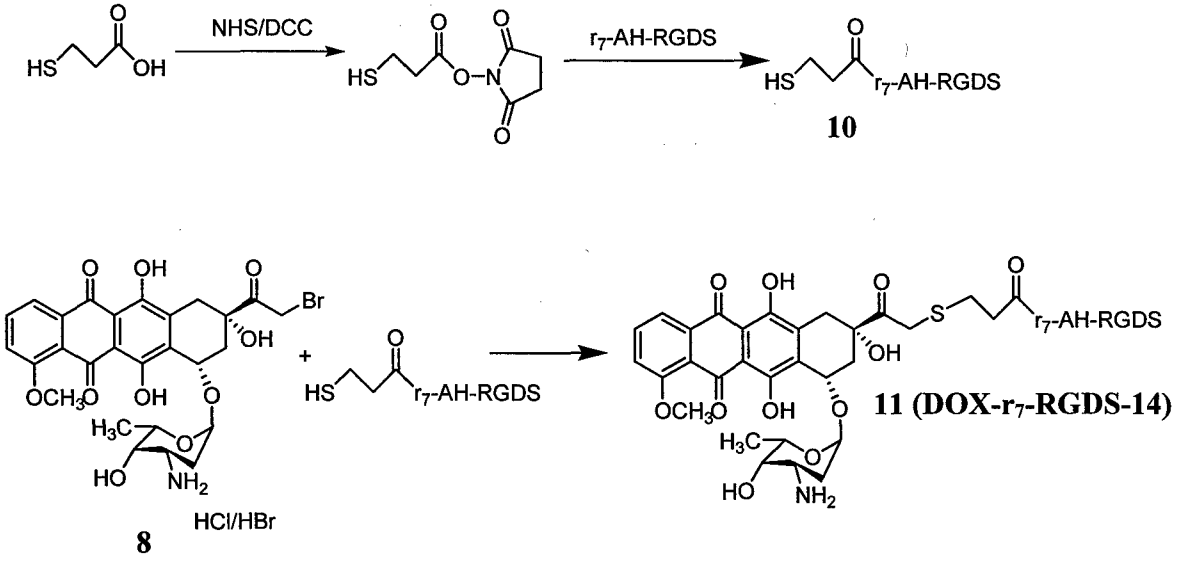
This reporting period we also returned to the preparation of DOX conjugates substituted at carbon-position 14. We anticipated an improvement in cancer cell cytotoxicity from these derivatives. Previous work has shown that C-14 substituted doxorubicin analogs to be more active that derivatives acylated on the amino sugar[2].

For these compounds we utilized the DOX C-14 bromo compound **8** (**Scheme 3**). Reaction of **8** with the thiol-r_7 peptide **4** led to DOX-r_7(C14) conjugate **9.**



Scheme 3

Similarly, bromo compound **8** was condensed with thiolated r_7-RGDS **10** giving the DOX-r_7-RGDS conjugate **11** (**Scheme 4**).



Task 2. Establish analytical approaches (confocal microscopy) to monitor the translocation of the doxorubicin conjugates into cells **(Months 9-24)**

Using the techniques developed last year, we employed the inherent fluorescence of doxorubicin, to follow the uptake of the newly synthesized conjugates into cancer cells. **Figure 2** shows fluorescent micrographs (400X) of the uptake of the compounds into MDA-MB-231 breast cancer cells. Conjugates (50 μM) were incubated with cells for 5 min and then observed. Compounds with a polyarginine as part of the conjugate accumulated in cells after 5 min, while free doxorubicin and the conjugate without a polyarginine did not appear to translocate into the cancer cells within this time.

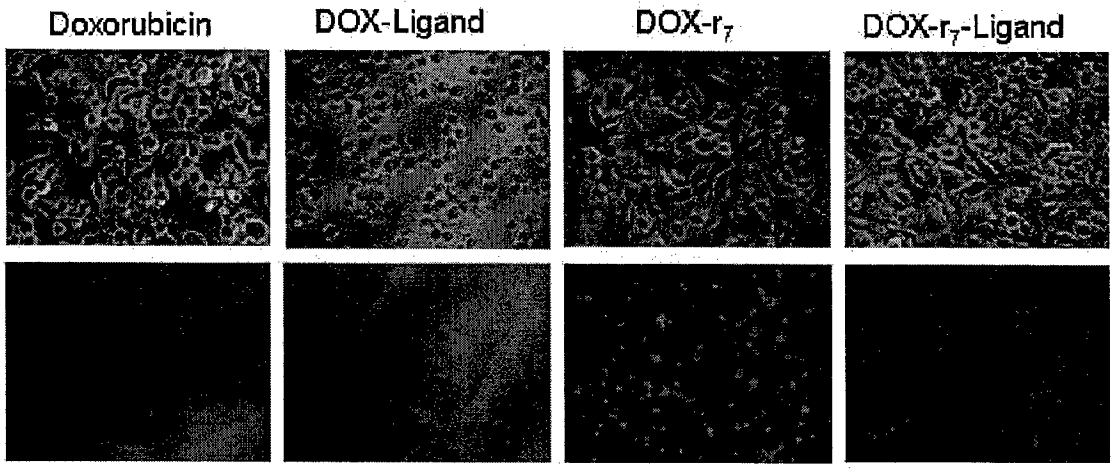


Figure 2

These results indicate the importance of the r_7 functionality for promoting rapid transport of the drug conjugates into cancer cells. The distribution of the DOX-r_7 conjugate into MDA-MB-231 breast cancer cells was also probed with fluorescence microscopy. As shown in **Figure 3** the conjugate remains localized in the cellular cytoplasm and does not appear to be effectively translocated into the nucleus. This may explain the lowered cytotoxic effects of the compound.

Figure 3. Distribution of Dox-r_7 in MDA-MB-231 cells. 50μM Dox-r_7 and 10μg/ml Hoescht 33342 nuclear stain were incubated with cells for 1 hour. The nuclei are blue and Dox-r_7 is red. Left: distribution of Dox-r_7. Right: conformation of minimal accumulation of Dox-r_7 in the nucleus area. Magnification 600X.

Task 3. Compare the cytotoxic efficacy of the drug conjugates (*vs.* free doxorubicin) in human breast cancer and normal breast cell lines **(Months 12-24).**

The new conjugates were evaluated for cytotoxicity against the $\alpha_V\beta_3$ expressing breast cancer cell-line MDA-MB-231 (**Figure 4**). After 24 hr exposure to the drugs, viable cells were assayed using the CyQuant™ cell proliferation assay (Molecular Probes, Eugene, OR). Most interesting about the results in **Figure 4** is that the activity of the DOX-r$_7$-Ligand compound compared to DOX-r$_7$-RGDS (See **Figure 1**). These data suggest that the higher affinity synthetic $\alpha_V\beta_3$ integrin ligand may be less favorable as the breast cancer cell targeting moiety for our targeted drug approach.

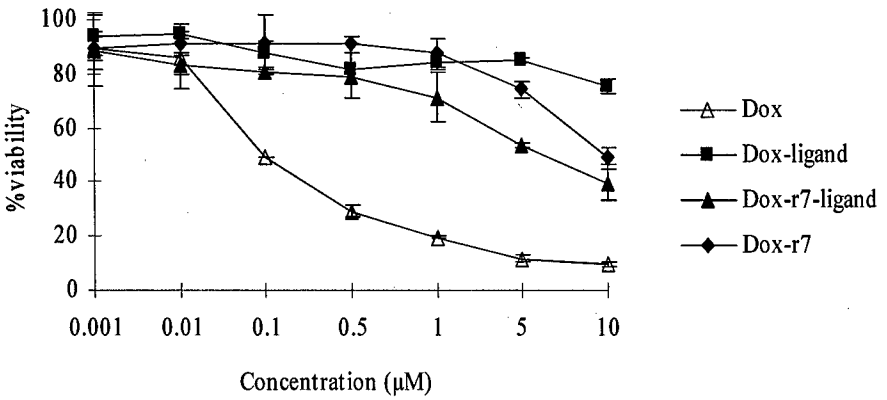


Figure 4. Cytotoxicity of conjugates against MDA-MB-231 cells. Viability of cells after incubation with the compounds for 72h.

This is supported by the results of preliminary cytotoxicity studies with the C-14 derivatized conjugates (**Figure 5**). In this case the RGDS conjugate has toxicity similar to the RGDS conjugate of **Figure 1**. A definitive comparison must await the synthesis and evaluation of the DOX-r$_7$-Ligand (14) conjugate.

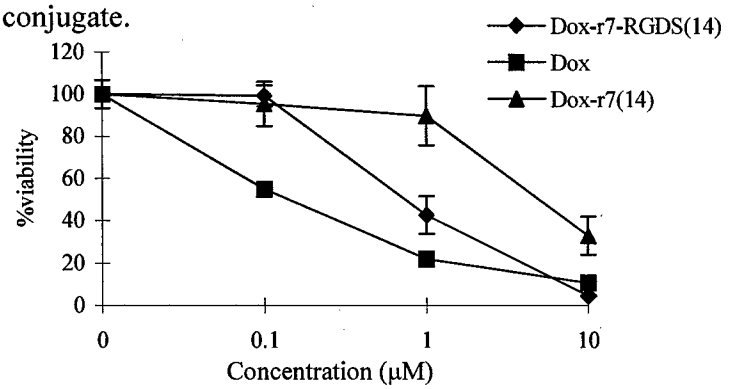


Figure 5. Cytotoxicity of C-14 position-modified drug conjugates against MDA-MB-231 cells. Viability of cells after incubation with the compounds for 72h

Task 4. Evaluate the efficacy of the conjugates (*vs.* free doxorubicin) in human breast cancer tumor xenografts in nude mice **(Months 24-36)**

This task is now scheduled for examination during the no cost program extension period.

C. Key Research Accomplishments

Key accomplishments from Year Three of this research are listed below.

- New doxorubicin conjugates have been prepared incorporating the [D-arginine]$_7$ cell membrane translocating functionality as well as a high affinity breast cancer cell targeting $\alpha_V\beta_3$ integrin ligand.
- All newly-synthesized compounds have been purified and chemically characterized.
- Several new conjugates have been evaluated for their effects on the breast cancer cell line MDA-MB-231.
- Ongoing experiments are examining the translocation of the conjugates into cancerous and non-cancerous cells as well as preparing to select the most active conjugate(s) for testing in a breast cancer xenograft mouse model.

D. Reportable Outcomes

This program supports graduate research assistant, Jiang Sha, and the results from the research will be incorporated into his dissertation. Postdoctoral research associate Hee-Kyoung Lee also assisted in this effort. A manuscript for the *Journal of Medicinal Chemistry* is in preparation outlining the synthesis of the compounds prepared to date and their effects in breast cancer cell lines.

E. Conclusions

Research on this effort thus far has provided modified doxorubicin intermediates suitable for attachment to a cell membrane translocating functionality and $\alpha_V\beta_3$ integrin targeting ligands. The resulting conjugates are being evaluated breast cancer cell culture experiments in order to ascertain cytotoxicity as well as selectivity for cancer cells over normal cells.

This research is significant in that it represents the first known examples of cancer chemotherapeutic agents incorporating a drug chemically linked both to a breast cancer-targeting moiety as well as a cell membrane translocating/nuclear localization functionality. The conjugates are expected to show selective targeting to breast cancer cells in preference to normal cells as well as exhibiting enhanced cancer cell cytotoxic effects. Preliminary results reported here are beginning to support the promising nature of this idea.

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(2) Arcamone, F., Doxorubicin, In: Anticancer Antibiotics; *Academic Press: New York, 1981; Vol. 17.*

G. Appendix

Biosketches

Jerald C. Hinshaw, Principal Investigator

Jiang Sha, Graduate Research Assistant

Hee-Kyoung Lee, Postdoctoral Associate

BIOGRAPHICAL SKETCH	
NAME **HINSHAW, JERALD CLYDE**	POSITION TITLE Research Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral trair*

INSTITUTION AND LOCATION	DEGRE	YEAR(s)	FIELD OF STUDY
Oregon State University, Corvallis, Oregon	BS	1966	Chemistry
The University of Utah, Salt Lake City, Utah	PhD	1970	Organic Chemistry

Research and Professional Experience:

1970-1978 Advanced from Senior Research Chemist to Research Associate, Organic Research Laboratory, Chemistry Division, Research Laboratories, Eastman Kodak Company

1978-1984 Scientist, Research and Development Laboratories, Thiokol Corporation

1980, 1986 Member, Utah Award Committee, Salt Lake Section, American Chemical Society

1981 Visiting Research Associate, University of Utah.

1981-1983 Chairman-Elect, Chairman, Past-Chairman, Salt Lake Section, American Chemical Society

1984-1990 Supervisor, Propellant Research Section, Research and Development Laboratories, Thiokol Corporation

1990-1999 Manager, Energetic Materials Research Department, Research and Development Laboratories,Thiokol Propulsion, Brigham City, Utah.

1996-1999 Member, State Advisory Council on Science and Technology (State of Utah, Governor appointment)

1997,1998 Member, Utah State Governor's Medal for Excellence in Science and Technology Award Committee

1997-1999 Chairman, State Advisory Council on Science and Technology (State of Utah, Governor appointment)

1997-1999 Member, Utah Centers of Excellence Program Advisory Council (State of Utah, Governor appointment)

2/99-7/99 Senior Staff to the Technical Director, Science and Engineering, Thiokol Propulsion, Brigham City, Utah

7/99-11/01 Research Assistant Professor, Department of Medicinal Chemistry, The University of Utah, Salt Lake City, Utah

11/01-current Research Associate Professor, Department of Medicinal Chemistry, The University of Utah, Salt Lake City, Utah

Research Interests:

Synthetic chemistry
Synthesis of bacterial oxidosqualene cyclase inhibitors
Cancer immunotherapy
Targeted drugs
Design and synthesis of small molecule inhibitors of protein-protein signaling
Research and technology management.

Honors:

Listed in "American Men and Women of Science"
Listed in "Who's Who in Technology"
Named Outstanding Senior in Chemistry, 1966
National Defense Education Act Title IV Fellow, 1968-1970
Franklin Award, Thiokol Corporation recognition for outstanding technical achievement, 1995

Publications/Patents: J. C. Hinshaw has over 50 publications and patents. A few are listed.

Ling Li and J.C. Hinshaw, "Synthesis of Photoprobes with Latent Fluorescence", *J. Amer. Chem. Soc.*, Manuscript in preparation.

J.C. Hinshaw, "Synthesis of Toll-Like Receptor-7 Ligand Immunostiumulating Conjugates", *Bioconjugate Chem,* Manuscript in preparation.

J.C. Hinshaw and Ling Li, "Breaking Immunological Self Tolerance", US Patent Application in preparation.

J.C. Hinshaw, Hee-Kyoung Lee, and Jiang Sha, "Targeted Cancer Drug Conjugates", US Patent Application in preparation.

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P. Y. Lum, C. D. Armour, S. B. Stepaniants, G. Cavet, A. Leonardson, P. Garrett-Engele, M. K. Wolf, L. Butler, C. M. Rush, M. Bard, J. C. Hinshaw, P. Garnier, G. D. Prestwich, G. Schimmack, J. W. Phillips, C. J. Roberts, and D. D. Shoemaker, "Discovering Novel Modes of Action for Therapeutic Compounds using a Genome-wide Screen of Yeast Heterozygotes," *Cell* 2004, **116**, 121-137.

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G. D. Prestwich, F. S. Buckner, J. C. Hinshaw, "Methods Related to Steroid Metabolism of Parasites and Mycobacteria, and Treatment of Parasite and Mycobacterial Infections with an Oxidosqualene Cyclase Inhibitor", U.S. Patent Application filed June 16, 2000.

R.B. Wardle, R.M. Hajik, J.C. Hinshaw, T.K. Highsmith, "Process for the Large-Scale Synthesis of 4,10-Dinitro-2,6,8,12-Tetraoxa-4,10-Diazatetracyclo[5.5.0.0]dodecane, "U.S. Patent 6,107,483, issued August 22, 2000.

J. C. Hinshaw, D. W. Doll, R. J. Blau, G. K. Lund, " Metal Complexes for Use as Gas Generants," U.S. Patent 6,039,820, issued March 21, 2000.

J. C. Hinshaw, D. W. Doll, R. J. Blau, G. K. Lund, "Metal Hydrazine Complexes Used as Gas Generants," U.S. Patent 5,970,703, issued October 26, 1999.

BIOGRAPHICAL SKETCH

Provide the following information for the Principal or Co-Principal Investigators
Follow this format for each person.

NAME	POSITION TITLE
Lee, Hee-Kyoung	Post-Doctoral Research Associate

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Seoul National University, Seoul, Korea	BS	1988	Chemistry
Seoul National University, Seoul, Korea	MS	1990	Biochemistry
Stony Brook University, New York, USA	Ph.D.	2004	Molecular Biology and Biochemistry

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Education and Experience

1984-1988 B.S. in Chemistry, Seoul National University, Seoul, Korea
General Advisor: Professor Hasuck Kim
Research Topic: *Characterization of Subtilisin from B. subtilis*

1988-1990 M.S. in Biochemistry, Seoul National University, Seoul, Korea
Research Advisor: Professor Chul-Hak Yang
Research Topic: *Cloning and Sequencing of Hydrogenase Gene from E. coli*

1990-1991 Full-time Teaching Assistant, Dept. of Chemistry, Seoul National University, Seoul, Korea

1991-1992 Full-time Teaching Assistant, Inter-University Instrument Facilities for Basic Science Research, Seoul National University, Seoul, Korea

1992-2003 Ph.D. in Molecular Biology & Biochemistry, Stony Brook University, New York.
Research Advisor: Professor Glenn D. Prestwich
Research Topic: *Molecular Interactions in Squalene Epoxidase: Photoaffinity Labeling and Mutagenesis Studies*

Publications

Pamela Denner-Ancona, Mei Bai, Hee-Kyoung Lee, Ikuro Abe and Glenn D. Prestwich, "Purification of Pig and Rat Liver Squalene Epoxidase by Affinity Chromatography" *Bioorg. Med. Chem. Lett.*, **5**, 481-486 (1995)

Hee-Kyoung Lee and Glenn D. Prestwich, "Unusual Signaling Pathway of Steroid Hormones: Dual Action of Progesterone" *Chemtracts,* **12**, 40-44 (1999)

Hee-Kyoung Lee, Pamela Denner-Ancona, Jun Sakakibara, Teruo Ono and Glenn D. Prestwich, "Photoaffinity Labeling and Site-Directed Mutagenesis of Rat Squalene Epoxidase" *Arch. Biochem. Biophys.*, **381**, 43-52 (2000)

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Hee-Kyoung Lee and J. C. Hinshaw, Breast Cancer Cell Targeted Drug Conjugates", *J. Med. Chem.*, Manuscript in preparation.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.

NAME	POSITION TITLE		
SHA, JIANG	Graduate Research Assistant		
EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*			
INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Peking University, Beijing, China	B.S.	1997-2001	Biology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Research and Professional Experience:

2000 - 2001 Institution of Biophysics, Chinese Academy of Science

2001 - 2002 Molecular Biology Program, The University of Utah, Laboratory Rotation

2002 - current Graduate Research Assistant, Department of Medicinal Chemistry, The University of Utah, Salt Lake City